☐ 1: Am J Reprod Immunol. 1993 Aug;30(1):1-8.

Transforming growth factor beta as an immunosuppressive pro in human seminal plasma.

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PROBLEM: Human seminal plasma is known to exhibit immunosuppressive activity in seminal plasma. PURPOSE: The purpose was to characterize immunosuppressive proteins in seminal plasma. METHOD: Gel filtration fractions of 100 to > 440 kDa were identified that inhibited DNA synthesis a killing activity of interleukin-2 stimulated lymphocytes. RESULTS: The fractions exhibiting immunosuppression also inhibited DNA synthesis in a m lung cell bioassay commonly used to measure the activity for transforming growth factor beta (TGF-beta). The negative growth activity was diminished a TGF-beta neutralizing monoclonal antibody. TGF-beta was further detecte the active fractions by Western immunoblot. CONCLUSIONS: These results identified TGF-beta as an immunosuppressive protein in human seminal plas and may provide insight into the role of immunosuppression played by semir plasma, such as in reproduction and neoplasia.

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☐ 1: Am J Reprod Immunol. 1989 Nov-Dec;21(3-4):147-50. Related Articles,

Immunological role for seminal plasma in insemination and pregnancy.

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Insemination confronts the female with paternally derived alloantigens and represents an immunological challenge preceding fertilization and implantati Current evidence suggests a role for seminal plasma in regulating maternal immunity for insemination and pregnancy. In vitro seminal plasma has been shown to suppress T- and B-cell proliferation, neutrophil and macrophage phagocytic activity, as well as killer cell activity. Seminal plasma interacts w complement components C1 and C3 and contains factors that specifically bir the Fc region of IgG. These in vitro findings suggest possible seminal plasma suppressive effects on female alloimmune responses after insemination. Sem plasma also contains allotypic TLX antigens that could prime mothers prior t fertilization. Such priming effects for pregnancy acceptance are supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transf treatment cycles.

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Reproductive immunology: Immunity's pregnant pause

If we can understand why a woman's body does not reject her fetus, it could help us to treat infertility and prevent problems in pregnancy. Helen Pearson reports.

In 1989, a young British woman had her ninth consecutive miscarriage. Her marriage broke down shortly afterwards. But within months of finding a new partner, she had conceived again and the pregnancy went without a hitch. Her daughter is now a healthy and lively nine-year-old.

Reproductive immunologists suspect that the woman's immune system took offence at her first choice of partner — over-reacting to tissues carrying his genes and expelling the fetuses he fathered. According to some experts, infertility, recurrent miscarriage, premature delivery and a dangerous complication of pregnancy called pre-eclampsia may all, in some cases, be linked to immunological abnormalities.

If these scientists are right, immunology could be reproductive medicine's next frontier, helping to treat distressing conditions that blight the lives of many couples. "This will be the new area of infertility treatment for this century," predicts Kelton Tremellen of the University of Adelaide in Australia.

Kelton Tremellen says IVF may be improved by preparing the way with proteins from semen.

In fact, how any fetus survives gestation has baffled scientists for decades: the embryo's tissues are half foreign and yet, unlike a mismatched organ transplant, it isn't normally rejected. Now researchers are revealing how different arms of the mother's immune system react to semen and the implanting embryo — and how the placenta protects itself from her immune system's attack. Some are already building from these findings to develop treatments that could help difficulties in conception and pregnancy. But there is also concern that rogue clinics may exploit preliminary results to offer couples therapies that have yet to be proved safe and effective.

The idea that the immune system may be to blame for problems with pregnancy stems in part from a long-standing observation about pre-eclampsia. This is a life-threatening condition for mother and child affecting up to one in ten pregnancies, in which the placental blood supply is insufficient and can starve a fetus of oxygen. First pregnancies are more susceptible to pre-eclampsia — unless a woman switches partner, in which case a second pregnancy is at equal risk. Previous exposure to a fetus carrying a particular suite of paternal genes, it seems, makes the immune system more likely to tolerate the first-born's subsequent siblings.

More recently, immunologists have wondered whether exposure to proteins in semen helps to prepare a woman's immune system for conception and pregnancy. Tremellen and his colleagues have studied one such protein, called TGF-β, found at high levels in semen. They injected TGF-β into a mouse's uterus alongside a cocktail of foreign proteins, and found that later injections of the same proteins under the skin did not elicit a strong immune reaction[1].

Tremellen, a gynaecologist working in the lab of reproductive immunologist Sarah Robertson at Adelaide, believes that 'immunization' with TGF-β through sexual intercourse helps the maternal

immune system learn to tolerate molecular signatures, or antigens, in semen by altering the production of inflammatory molecules called cytokines. He has already shown that *in vitro* fertilization (IVF) is more successful if couples have sex beforehand[2], and hopes soon to begin trials of a vaginal TGF-β gel to see if it can help women suffering recurrent miscarriage.

Although proteins in semen may smooth the way for a future baby, damping down a mother's immune response to the implanting embryo also seems to be crucial to a pregnancy's success. At implantation, a group of embryonic cells called the trophoblast aggressively invades the mother's uterus lining, anchoring the placenta and widening the maternal arteries to enhance its blood supply.

Ashley Moffett-King of the University of Cambridge, UK, and her team have found that natural killer (NK) cells flood the uterus at this time. These immune cells are usually involved in attacking cancerous or virus-infected cells. But those drawn to the uterus at implantation carry receptors that interact with two unusual antigens, HLA-C and HLA-E, on the surface of trophoblast cells.

Exactly what happens as a result of the interaction between NK cells and the trophoblast is still subject to debate[3]. Moffett-King suspects that it triggers the production of particular cytokines that either help the trophoblast to invade the uterine wall or limit the extent to which it invades. When this process goes wrong, she suggests, the fetal blood supply is compromised and pre-eclampsia might result. If so, a mismatch between HLA antigens on the fetal cells and receptors on the mother's NK cells might predispose certain women to the condition. Moffett-King is now embarking on a study to search for susceptible combinations in 300 British women.

Fetal distraction

Other researchers have discovered several ways in which embryonic tissues disable the mother's immune system — including secreting suppressive factors into her blood or displaying them on placental cells. Another antigen called HLA-G, for example, is released from the trophoblast into the mother's bloodstream, and seems to protect the trophoblast from attack. Researchers led by Philippe Le Bouteiller, who works for INSERM, France's medical research agency, at the Purpan Hospital in Toulouse, have recently shown that soluble HLA-G makes certain types of immune-system T cell — which may attack fetal cells bearing the father's antigens — commit suicide[4]. What's more, a team led by Olavio Baricordi at the University of Ferrara in Italy recently found that implantation after IVF only occurred if the embryos secreted soluble HLA-G (ref. 5).

Based on such findings, Joan Hunt of the University of Kansas Medical Center in Kansas City has already patented a genetically engineered form of human HLA-G. "It could be administered to women with fertility problems," she suggests.

Last year, George Chrousos of the National Institute of Child Health and Human Development in Bethesda, Maryland, presented further evidence that a developing fetus induces some of its mother's T cells to commit suicide. His team showed that corticotropin-releasing hormone (CRH), which is secreted by both the implanting embryo and the lining of the uterus, stimulates trophoblast cells to produce a molecule, known as the Fas ligand, that binds to a cell-surface receptor that triggers cell death. When T cells were grown together with trophoblast cells stimulated by CRH, they died[6].

Andrew Mellor (left) and George

Later in pregnancy, CRH seems to have an inflammatory role

that helps to trigger labour. Chrousos has identified a molecule called antalarmin that blocks the action of CRH (ref. 6), and in unpublished work he found that it seems to delay labour in sheep.

Chrousos are tracing how a fetus hampers its mother's immune system.

Andrew Mellor of the Medical College of Georgia in Augusta, meanwhile, believes that the placenta cripples maternal T cells in another way: by starving them. In 1998, his team showed that the mouse placenta makes an enzyme called indoleamine 2,3-dioxygenase (IDO), which breaks down an amino acid called tryptophan that is vital for T cells' nutrition. Injections of a molecule that blocks IDO caused high rates of abortion in mice, the team found[7]. "The simple prediction is that problem pregnancies are associated with variations in the IDO gene," says Mellor — although its role in human pregnancy has yet to be demonstrated.

More recently, Mellor's team has shown that the fetal rejection triggered in mice by blocking IDO activates an arm of the immune system called complement[8]. This series of blood plasma proteins is one of the first lines of defence against bacterial and viral infections. But Hector Molina of Washington University in St Louis has shown that it can also hinder pregnancy. Molina's group found that mice lacking Crry, a cell-surface protein that protects tissues against misdirected complement activation, lose their fetuses[9]. Molina now plans to study whether women suffering recurrent miscarriage or pre-term labour have altered levels of proteins that mediate complement, or mutations in the human equivalent of the gene for Crry.

Birth control

With each researcher advocating their favoured mechanism for sustaining gestation, it will be some time before a complete picture emerges. But most agree that mother and fetus use several means in parallel to bring about a peaceful nine months. "There's no definite gene required for gestation," says Mellor. "But if you take one out there's more risk that a pregnancy will be lost."

The eventual goal is to convert the growing knowledge of reproductive immunology into treatments for infertility, miscarriage and other complications of pregnancy. Here, the field's pioneers are battling not only scientific and clinical complexities, but also practitioners operating at the fringes of reproductive medicine who are willing to offer highly speculative 'treatments' to couples desperate to have a baby.

Since the 1980s, for example, women suffering recurrent miscarriage have been offered injections of their partner's white blood cells, supposedly to prime their immune system into accepting a fetus bearing his antigens. Researchers have protested that this is not based on good evidence, and they have been vindicated by a negative randomized clinical trial[10].

Disturbingly, some US doctors are now offering diagnostic tests to determine whether the NK cells in the mother's circulation are abnormal, even though this may be of little relevance to the interactions in the placenta being studied by Moffett-King.

"People try to get the clinical solutions before the science is worked out," says Ian Sargent, an immunologist at the University of Oxford, UK. "It has dogged this area."

HELEN PEARSON
Helen Pearson works in Nature's news syndication team.

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Articles

Mononuclear-cell immunisation in prevention of recurrent miscarriages: a randomised trial

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Available online 30 August 1999.

Abstract

Background Couples with unexplained recurrent miscarriage may have an alloimmune abnormality that prevents the mother from developing immune responses essential for the survival of the genetically foreign conceptus. Immunisation with paternal mononuclear cells is used as a treatment for such alloimmune-mediated pregnancy losses. However, the published results on this treatment are conflicting. In this study (the Recurrent Miscarriage [REMIS] Study), we investigated whether paternal mononuclear cell immunisation improves the rate of successful pregnancies.

Methods Women who had had three or more spontaneous abortions of unknown cause were enrolled in a double-blind, multicentre, randomised clinical trial. 91 were assigned immunisation with paternal mononuclear cells (treatment) and 92 immunisation with sterile saline (control). The primary outcomes were the inability to achieve pregnancy within 12 months of randomisation, or a pregnancy which terminated before 28 weeks of gestation (failure); and pregnancy of 28 or more weeks of gestation (success). Two analyses were done: one included all women (intention to treat), and the other included only those who became pregnant.

Findings Two women in each group received no treatment, and eight (three treatment, five control) were censored after an interim analysis. In the analysis of all randomised women who completed the trial, the success rate was 31/86 (36%) in the treatment group and 41/85 (48%) in the control group (odds ratio 0·60 [95% CI 0·33–1·12], p=0·108). In the analysis of pregnant women only, the corresponding success rates were 31/68 (46%) and 41/63 (65%; odds ratio 0·45 [0·22–0·91], p=0·026). The results were unchanged after adjustment for maternal age, number of previous miscarriages, and whether or not the couple had had a previous viable pregnancy. Similar results were obtained in a subgroup analysis of 133 couples with no previous livebirth.

Interpretation Immunisation with paternal mononuclear cells does not improve pregnancy outcome in women with unexplained recurrent miscarriage. This therapy should not be offered as a treatment for pregnancy loss.

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☐ 1: Hum Reprod. 1997 Oct;12(10):2200-7.

Immunomodulation by human seminal plasma: a benefit for spermatozoon and pathogen?

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The immunosuppressive effect of human seminal plasma and its implications
sperm survival are reviewed. Human semen contains high concentrations of
prostaglandins that can effect a cytokine-mediated switch away from a cell-
mediated immune response. This effect on antigen presenting cells would inc
a state of non-responsiveness to sperm antigens in the female reproductive tr
It is postulated that the induction of anergy to sperm antigen may be
fundamental to the continuing fecundity of the individual. However, althougl
this immune system modulation will benefit the spermatozoa, the response tc
infective agents present in semen will also be affected, which may play a crit
role in the aetiology and progress of sexually transmitted disease.

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